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Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

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Please search the methods and composition of claims 1-12, 19, 20, 23, and 25-38. For the initial search, please limit the search of generic claims 1-12 and 25-38 to the agents specifically set forth in claims 19, 20, and 23. This is another election of species otherwise will have to extend the search (mail me) if you don't find anything.

Inventors: Denise D. WAGNER
Robert C. JOHNSON

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=> fil wpids
FILE 'WPIDS' ENTERED AT 12:54:57 ON 27 FEB 96
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DERWENT WEEK FOR POLYMER INDEXING:      9603
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               E WAGNER D/AU
L1          113 S E3,E7
               E JOHNSON R/AU
L2          120 S E3,E6
L3            1 S L1 AND L2
               SEL L3 PN APPS

     FILE 'HCAPLUS' ENTERED AT 12:54:43 ON 27 FEB 96
L4            1 S E1-E4

     FILE 'WPIDS' ENTERED AT 12:54:57 ON 27 FEB 96

=> d l3 bib abs

L3   ANSWER 1 OF 1  WPIDS   COPYRIGHT 1996 DERWENT INFORMATION LTD
AN   96-039970 [04]   WPIDS
DNC  C96-013421
TI   Treatment or prevention of atherosclerosis - using agent that
     inhibits interaction between P-selectin and its ligand.
DC   B04 D16
IN   JOHNSON, R C; WAGNER, D D
PA   (BLOO-N) CENT BLOOD RES INC
CYC  18
PI   WO 9533484  A1 951214 (9604)* EN   35 pp
        RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
         W: CA JP
ADT  WO 9533484 A1 WO 95-US6940 950601
PRAI US 95-377798   950124; US 94-253663   940603
AN   96-039970 [04]   WPIDS
AB   WO 9533484 A   UPAB: 960129
     Treatment or prevention of atherosclerosis in a mammal comprises the
     admin. of an agent (I) that inhibits interaction between P-selectin
     (PS) and its ligand (L).
          USE - (I) can be used on a human to prevent ( partially) the
     formation of an atherosclerotic fatty streak, intermediate lesion,
     fibrous plaque or regrowth of a lesion after surgery (prevention of
     restenosis), it may also (partially) eliminate such lesions, plaques
     and fatty streaks that have already formed (claimed). Typically (I)
     is admin. at 0.1-500 mg/kg given e.g. orally, topically, as an
     implant, by injection or inhalation.
          ADVANTAGE - Treatment with (I) is safe, efficient, easy,
     inexpensive and non-invasive. (I) may have a reversible effect, i.e.
     when admin. ceases, PS function (involved in the response to
     infection and injury) is restored.
     Dwg.0/0

=> fil hcaplus
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FILE COVERS 1967 - 27 Feb 1996 VOL 124 ISS 9
FILE LAST UPDATED: 28 Feb 1996 (960228/ED)

=> d l4 all

L4 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 1996 ACS
AN 1996:106553 HCAPLUS
TI Method using agents inhibiting interaction between P-selectin??? and a P-selectin ligand for treating and preventing atherosclerosis
IN Wagner, Denisa D.; Johnson, Robert C.
PA Center for Blood Research, Inc., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PI **WO 9533484 A1** 951214
DS W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI **WO 95-US6940** 950601
PRAI **US 94-253663** 940603
US 95-377798 950124
DT Patent
LA English
IC ICM A61K039-395
ICS A61K038-02; A61K038-16; A61K031-70
CC 1 (Pharmacology)
AB A method for treating or preventing atherosclerosis in a mammal is described. An agent for inhibiting interaction between P-selectin and a ligand of P-selectin is provided. The agent is administered to a mammal in need of such treatment to cause this inhibition to occur.
IT RN LIST MAY NOT BE COMPLETE: 9005-49-6

=> d his l6-

(FILE 'EMBASE' ENTERED AT 12:55:53 ON 27 FEB 96)
E WAGNER D/AU
L6 161 S E3,E7
E JOHNSON R/AU
L7 665 S E3,E8
L8 4 S L6 AND L7
L9 462 S PADGEM PROTEIN/CT
L10 25444 S ATHEROSCLEROSIS+NT/CT
L11 17 S L9 AND L10
L12 262 S L9/MAJ
L13 8 S L12 AND L10
L14 9 S L11 NOT L13
L15 1 S L11 AND D4.140.140./CT
L16 0 S L11 AND CARBOHYDRATE DERIVATIVE+NT/CT
L17 0 S L11 AND HEPARIN/CT
L18 0 S L11 AND SULFATIDE/CT
L19 21 S L8 OR L11

FILE 'MEDLINE' ENTERED AT 13:02:48 ON 27 FEB 96
E WAGNER D/AU
L20 209 S E3,E6
E JOHNSON R/AU
L21 833 S E3,E8
L22 3 S L20 AND L21
L23 41074 S ARTERIOSCLEROSIS+NT/CT
L24 4 S L23 AND P SELECTIN
L25 2835 S PLATELET MEMBRANE GLYCOPROTEINS/CT
L26 9 S L23 AND L25
L27 7 S L22 OR L24
L28 6 S L26 NOT L27
L29 2948 S L23 AND D9./CT
L30 57 S L23 AND NEURAMINIC ACIDS+NT/CT
L31 9 S L23 AND CEREBROSIDES+NT/CT

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L32          478 S L23 AND HEPARIN+NT/CT
L33            0 S L23 AND ("5-ACETYLNEURAMINYL-(2-3)-GALACTOSYL-(1-4)-(FU
L34            1 S L25 AND (L29 OR L30 OR L31 OR L32)
L35            0 S L34 AND SELECTIN

     FILE 'EMBASE, MEDLINE' ENTERED AT 13:11:39 ON 27 FEB 96
L36           23 DUP REM L19 L27 (5 DUPLICATES REMOVED)

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                E WAGNER D/AU
L37          269 S E3,E7
                E JOHNSON R/AU
L38         1378 S E3,E9-E11
L39            3 S L37 AND L38

     FILE 'HCAPLUS' ENTERED AT 13:12:19 ON 27 FEB 96
L40        16554 S (ATHEROSCLERO? OR ARTERIOSCLERO?)/BI,AB
L41          529 S (P()(SELECTIN OR SELECTINS))/BI,AB
L42          219 S (PADGEM OR LECAM()3 OR GMP140 OR GMP 140)/BI,AB
L43           19 S L40 AND L41
L44            8 S L40 AND L42
L45           21 S L43 OR L44
L46         1657 S (PLATELET# (L) GRANULE#)/BI,AB
L47         3454 S (PLATELET# (L) MEMBRANE# (L) (GLYCOPROTEIN# OR PROTEIN#
L48           21 S L40 AND L46
L49           31 S L40 AND L47
L50           62 S L43 OR L44 OR L45 OR L48 OR L49
L51            2 S L50 AND (SIALIC OR SULFATIDE# OR HEPARIN#)/BI,AB
L52            2 S L50 AND (LEWIS OR LEX OR LEA OR LE()(X OR A))/BI,AB
L53            1 S L50 AND SIALYL/BI,AB
                E WAGNER D/AU
L54          211 S E3,E6,E63-E65
                E JOHNSON R/AU
L55          258 S E3,E8,E9
                E JOHNSON ROBERT/AU
L56          108 S E3,E12-E18
L57            5 S L54 AND (L55 OR L56)
L58           26 S L45 OR L51 OR L52 OR L53 OR L57
                E LIGAND/CT
L59         6137 S E4
L60           10 S L59 AND (L41 OR L42)
                E GLYCOPROTEIN/CT
L61        48758 S E2-E24
L62          814 S L61 (L) (SELECTIN OR SELECTINS)/BI
L63           19 S L62 AND L59
L64            1 S L40 AND L63
L65           46 S L58 OR L60 OR L63 OR L64

     FILE 'HCAPLUS, BIOSIS, MEDLINE, EMBASE' ENTERED AT 13:27:29 ON 27
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L66           61 DUP REM L65 L39 L27 L19 (16 DUPLICATES REMOVED)

=> fil hcaplus biosis medline embase
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FILE 'MEDLINE' ENTERED AT 13:28:01 ON 27 FEB 96

FILE 'EMBASE' ENTERED AT 13:28:01 ON 27 FEB 96
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=> d l66 1-61 cbib ab

L66  ANSWER 1 OF 61  HCAPLUS  COPYRIGHT 1996 ACS
1996:105459  Defects in hemostasis in P-selectin - deficient mice.
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Subramaniam, Meera; Frenette, Paul S.; Saffaripour, Simin; **Johnson, Robert C.**; Hynes, Richard O.; **Wagner, Denisa D.** (Center for Blood Research, Harvard Medical School, Boston, Mass., MA, USA). Blood, 87(4), 1238-42 (English) 1996. CODEN: BLOOAW. ISSN: 0006-4971.

AB Recently, our lab. showed that platelets, like leukocytes, roll on activated endothelium expressing P-selectin, thus suggesting a role for P-selectin in hemostasis. We report here that the P-selectin-deficient mice show a 40% prolongation of the bleeding time on amputation of the tip of the tail. Moreover, defective hemostasis was obsd. in a local Shwartzman-like reaction induced by skin injections of lipopolysaccharide followed by tumor necrosis factor-.alpha. in the P-selectin-deficient mice. The hemorrhagic lesions, quantitated both macroscopically and microscopically, were 2-fold larger in the P-selectin-deficient mice. This was also confirmed by measuring the radioactivity in the skin using chromium-labeled red blood cells. Therefore, it is evident that P-selectin plays a role in hemostasis as suggested by its support of platelet rolling.

L66 ANSWER 2 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.

96037970 EMBASE Hypoxia-induced exocytosis of endothelial cell Weibel-Palade bodies. A mechanism for rapid neutrophil recruitment after cardiac preservation. Pinsky D.J.; Naka Y.; Liao H.; Oz M.C.; **Wagner D.D.**; Mayadas T.N.; **Johnson R.C.**; Hynes R.O.; Heath M.; Lawson C.A.; Stern D.M.. Department of Medicine, Columbia University, 630 W. 168 Street, New York, NY 10032, United States. Journal of Clinical Investigation 97/2 (493-500) 1996. ISSN: 0021-9738. CODEN: JCINAO. Pub. Country: United States. Language: English. Summary Language: English.

AB The period of hypoxia is an important priming event for the vascular dysfunction that accompanies reperfusion, with endothelial cells (ECs) and neutrophils (PMNs) playing a central role. We hypothesized that EC Weibel-Palade (WP) body exocytosis during the hypoxic/ischemic period during organ preservation permits brisk PMN recruitment into postischemic tissue, a process further amplified in an oxidant-rich milieu. Exposure of human umbilical vein ECs to a hypoxic environment (pO2 .simeq. 20 torr) stimulated release of yon Willebrand factor (vWF), stored in EC WP bodies, as well as increased expression of the WP body-derived PMN adhesion molecule P-selectin at the EC surface. Increased binding of 111In- labeled PMNs to hypoxic EC monolayers (compared with normoxic controls) was blocked with a blocking antibody to P-selectin, but was not affected by a nonblocking control antibody. Although increased P-selectin expression and vWF release were also noted during reoxygenation, hypoxia alone (even in the presence of antioxidants) was sufficient to increase WP body exocytosis. To determine the relevance of these observations to hypothermic cardiac preservation, during which the pO2 within the cardiac vasculature declines to similarly low levels, experiments were performed in a rodent (rat and mouse) cardiac preservation/transplantation model. Immunodepletion of recipient PMNs or administration of a blocking anti-P-selectin antibody before transplantation resulted in reduced graft neutrophil infiltration and improved graft survival, compared with identically preserved hearts transplanted into control recipients. To establish the important role of endothelial P-selectin expression on the donor vasculature, murine cardiac transplants were performed using homozygous P-selectin deficient and wild-type control donor hearts flushed free of blood/platelets before preservation/transplantation. P-selectin-null hearts transplanted into wild-type recipients demonstrated a marked (13-fold) reduction in graft neutrophil infiltration and increased graft survival compared with wild-type hearts transplanted into wild-type recipients. To determine whether coronary endothelial WP exocytosis may occur during cardiac preservation in humans, the release of vWF into the coronary sinus (CS) was measured in 32 patients during open heart surgery. CS samples obtained at the start and conclusion of the ischemic period demonstrated an increase in CS vWF antigen (by ELISA) consisting of predominantly high molecular weight multimers (by

immunoelectrophoresis). These data suggest that EC WP exocytosis occurs during hypothermic cardiac preservation, priming the vasculature to recruit PMNs rapidly during reperfusion.

L66 ANSWER 3 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1996:54133 Document No. 124:109811 Selectins and their ligands. Watson, Susan R. (Department Immunology, Genetech, Inc., South San Francisco, CA, USA). Adhes. Recept. Ther. Targets, 61-73. Editor(s): Horton, Michael A. CRC: Boca Raton, Fla. (English) 1996. CODEN: 62EZAF.
AB A review, with 105 refs., on the selectin family of adhesion mols., their structure and their role in rolling, approaches to identifying selectin ligands, carbohydrate ligands of selectins, modulation of L-selectin ligands, MAdCAM-1 as a versatile ligand, ligands for E- and **P-selectin**, and therapeutic potential for selectins.

L66 ANSWER 4 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
96004679 EMBASE DNA polymorphisms in adhesion molecule genes a new risk factor for early atherosclerosis. Wenzel K.; Ernst M.; Rohde K.; Baumann G.; Speer A.. Department of Internal Medicine I, Division of Molecular Biology, Charite, Ziegelstrasse 5-9, D-10117 Berlin, Germany, Federal Republic of. Human Genetics 97/1 (15-20) 1996. ISSN: 0340-6717. CODEN: HUGEDQ. Pub. Country: Germany, Federal Republic of. Language: English. Summary Language: English.
AB To contribute to the analysis of the genetic background of atherosclerosis, especially endothelial dysfunction, we searched for DNA polymorphisms in the genes encoding E-, P-, and L-selectin, and ICAM-I and VCAM-I. We detected 17 mutations by single-strand conformation polymorphisms analysis and direct sequencing. Five of them resulted in an amino acid substitution. In E-selectin, exchanges from serine to arginine (position 128), from leucine to phenylalanine (position 554), and a DNA mutation from guanine to thymine (position 98) present significantly different allele frequencies in young patients with angiographically established, severe atherosclerosis, compared with an unselected population. Results suggest that these polymorphisms are associated with a higher risk for early severe atherosclerosis.

L66 ANSWER 5 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1996:106553 Method using agents inhibiting interaction between **P-selectin**??? and a **P-selectin** ligand for treating and preventing **atherosclerosis**. **Wagner, Denisa D.**; **Johnson, Robert C.** (Center for Blood Research, Inc., USA). PCT Int. Appl. WO 9533484 A1 951214, 35 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 95-US6940 950601. PRIORITY: US 94-253663 940603; US 95-377798 950124.
AB A method for treating or preventing **atherosclerosis** in a mammal is described. An agent for inhibiting interaction between **P-selectin** and a ligand of **P-selectin** is provided. The agent is administered to a mammal in need of such treatment to cause this inhibition to occur.

L66 ANSWER 6 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 1
1995:736586 Document No. 123:140072 Platelets roll on stimulated endothelium in vivo: an interaction mediated by endothelial P-selectin. Frenette, Paul S.; **Johnson, Robert C.**; Hynes, Richard O.; **Wagner, Denisa D.** (Dep. Pathol., Harvard Med. Sch., Boston, MA, 02115, USA). Proc. Natl. Acad. Sci. U. S. A., 92(16), 7450-4 (English) 1995. CODEN: PNASA6. ISSN: 0027-8424.
AB P-selectin, found in storage granules of platelets and endothelial cells, can be rapidly expressed upon stimulation. Mice lacking this membrane receptor exhibit a severe impairment of leukocyte rolling. It was obsd. that, in addn. to leukocytes, platelets were rolling in mesenteric venules of wild-type mice. To investigate the role of P-selectin in this process, resting or activated platelets from wild-type or P-selectin-deficient mice were fluorescently labeled

and transfused into recipients of either genotype. Platelets-endothelial interactions were monitored by intravital microscopy. Rolling was obsd. for either wild-type or P-selectin-deficient resting platelets on wild-type endothelium. Endothelial stimulation with the calcium ionophore A23187 increased the no. of platelets rolling 4-fold. Activated P-selectin-deficient platelets behaved similarly, whereas activated wild-type platelets bound to leukocytes and were seen rolling together. Platelets of either genotype, resting or activated, interacted minimally with mutant endothelium even after A23187 treatment. The velocity of platelet rolling was 6-9-fold greater than that of leukocytes. Results demonstrate that (1) platelets roll on endothelium in vivo, (2) this interaction requires endothelial but not platelet P-selectin, and (3) platelet rolling appears to be independent of platelet activation, indicating constitutive expression of a P-selectin ligand(s) on platelets. Thus, an interesting parallel was obsd. between platelets and leukocytes in that both of these blood cell types roll on stimulated vessel wall and that this process is dependent on the expression of endothelial P-selectin.

L66 ANSWER 7 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
95161894 EMBASE Reactive oxygen intermediates induce regulated secretion of von Willebrand factor from cultured human vascular endothelial cells. Vischer U.M.; Jornot L.; Wollheim C.B.; Theler J.-M.. Division de Biochimie Clinique, Centre Medical Universitaire, 1 rue Michel Servet, 1211 Geneva 4, Switzerland. Blood 85/11 (3164-3172) 1995. ISSN: 0006-4971. CODEN: BLOOAW. Pub. Country: United States. Language: English. Summary Language: English.

AB Exocytosis from Weibel-Palade bodies, the secretory granules of vascular endothelial cells, causes the rapid release of yon Willebrand factor (vWF), an adhesive glycoprotein involved in primary hemostasis, and cell surface expression of P-selectin, a membrane protein involved in neutrophil binding. Thus, exocytosis may represent a link between hemostasis and inflammation. We investigated the effect of reactive oxygen intermediates (ROIs) on vWF secretion. Incubation of cultured endothelial cells with xanthine oxidase (XO), which generates superoxide anions (O2-), induces a potent, rapid secretory response. However, vWF release was not observed in response to H2O2. Extracellular, subendothelial vWF deposits typically seen after exocytosis from Weibel-Palade bodies were observed after exposure to XO. XO caused a rapid, sustained increase in intracellular free calcium concentration ([Ca2+](i)). vWF secretion was markedly inhibited by BAPTA- AM, a cell-permeant calcium chelator. Removal of extracellular calcium did not inhibit vWF release, although the sustained phase of the [Ca2+](i) increase was suppressed. These results suggest that XO-induced vWF release is mediated by the initial increase in [Ca2+](i) which is caused by calcium mobilization from intracellular stores rather than by calcium influx. Exocytosis from Weibel-Palade bodies may contribute to the pathogenic effect of ROIs in atherosclerosis and inflammation.

L66 ANSWER 8 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
95247379 EMBASE P-selectin regulates platelet-activating factor synthesis and phagocytosis by monocytes. Elstad M.R.; La Pine T.R.; Cowley F.S.; McEver R.P.; McIntyre T.M.; Prescott S.M.; Zimmerman G.A.. CVRTI, Bldg. 500, University of Utah, Salt Lake City, UT 84112, United States. Journal of Immunology 155/4 (2109-2122) 1995. ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB Adhesion molecules on endothelial cells or platelets may regulate localization and activation of leukocytes at sites of tissue injury, infection, or thrombosis. In these studies, we found that human peripheral blood monocytes adhered specifically to immobilized P-selectin (CD62P), Chinese hamster ovary cells transfected with a cDNA for P-selectin, or endothelial cells stimulated to express P-selectin on the cell surface. P- selectin did not directly stimulate synthesis of the lipid autacoid platelet- activating factor (PAF); however, incubation on immobilized P-selectin primed

monocytes for increased synthesis of PAF in response to opsonized zymosan particles. P-selectin did not stimulate increased surface expression of integrin CD11b/CD18 and did not enhance binding of iC3b-coated erythrocytes, a CD11b/CD18-mediated functional response. P-selectin increased PAF production by monocytes incubated with unopsonized zymosan particles that stimulate this response by interaction with the .beta.-glucan receptor. Further, phagocytosis of unopsonized zymosan particles, another response triggered by the .beta.-glucan receptor, was increased following the adherence of monocytes to P-selectin. These data suggested that P-selectin primed monocytes for increased PAF synthesis through regulation of the .beta.-glucan receptor or regulation of signal transduction mechanisms that are linked to the receptor. P-selectin expressed on endothelial cells or platelets may serve both to localize monocytes at sites of vascular inflammation or thrombosis and to prime the cells for subsequent responses that augment inflammation.

L66 ANSWER 9 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
95341525 EMBASE Oxidized low-density lipoproteins facilitate leukocyte adhesion to aortic intima without affecting endothelium-dependent relaxation: Role of P-selectin. Mehta A.; Yang B.; Khan S.; Hendricks J.B.; Stephen C.; Mehta J.L.. University of Florida, JHMHC, Box 100277, Gainesville, FL 32610, United States. Arteriosclerosis, Thrombosis, and Vascular Biology 15/11 (2076-2083) 1995. ISSN: 1079-5642. CODEN: ATVBFA. Pub. Country: United States. Language: English. Summary Language: English.

AB Inflammatory cell deposition in atherosclerotic blood vessels has been thought to relate to loss of endothelium-derived nitric oxide (NO). To examine whether cell deposition correlates temporally with the loss of NO activity, rat aortic rings were incubated with buffer, native LDL (n-LDL), oxidized LDL (ox-LDL), or the endothelium-derived relaxing factor synthase inhibitor N(.omega.)-nitro-L-arginine methyl ester (L-NAME) for 2 hours, and vascular contractile response to norepinephrine and relaxant response to acetylcholine, thrombin, and calcium ionophore A23,187 were examined. Thereafter, the rings were exposed to biotin-fluorescein isothiocyanate labeled fluorescent or unlabeled leukocytes for 30 minutes. Cell adhesion was quantitated by fluorescent microscopy as well as by scanning electron microscopy. Incubation with n-LDL or ox-LDL did not affect either the contractile or the relaxant response of rings. However, leukocyte adhesion increased markedly in all ox-LDL-treated rings but not in those treated with n-LSL. Thus, leukocyte adhesion occurred independent of NO activity. In keeping with this concept, pretreatment of rings with the NO precursor L- arginine failed to influence leukocyte adhesion to rings incubated with ox- LDL. Treatment of rings with L-NAME also resulted in adhesion of a large number of leukocytes. Furthermore, all rings treated with ox-LDL or L-NAME demonstrated marked expression of P-selectin leukocyte adhesion molecules, determined by immunohistochemistry. Pretreatment of rings with the P-selectin blocking antibody PBL3 markedly decreased deposition of leukocytes in rings exposed to ox-LDL. These data show that cell adhesion to vascular intima exposed to ox-LDL shows no temporal relation with attenuation of NO activity, although inhibition of NO synthesis leads to leukocyte deposition. P-selectin expression on vascular rings exposed to ox-LDL appears to be the basis of leukocyte deposition.

L66 ANSWER 10 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
96021733 EMBASE Soluble adhesion molecule P-selectin and endothelial dysfunction in essential hypertension: Implications for atherogenesis? A preliminary report. Lip G.Y.H.; Blann A.D.; Zarifis J.; Beevers M.; Lip P.-L.; Beevers D.G.. University Department of Medicine, City Hospital, Dudley Road, Birmingham B18 7QH, United Kingdom. Journal of Hypertension 13/12 II (1674-1678) 1995. ISSN: 0263-6352. CODEN: JOHYD3. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Objective: Patients with essential hypertension are at high risk of atherosclerotic vascular disease. To investigate this further, we

measured levels of the soluble adhesion molecule P-selectin, which is associated with platelet activity/function and atherosclerosis, von Willebrand factor, which is a marker of endothelial dysfunction, and plasma fibrinogen. Patients and methods: We studied 104 consecutive patients (47 males, 57 females; mean .+-. SD age 54.8 .+-. 14.1 years) with essential hypertension compared with 47 normotensive healthy controls (55.0 .+-. 19.2 years). Levels of soluble adhesion molecule P-selectin and von Willebrand factor were measured by enzyme-linked immunosorbent assay, and plasma fibrinogen by a clotting method (CLAUSS). Results: Compared with normotensives, the hypertensives showed significant increases in soluble P-selectin (300 versus 228 ng/ml; median difference 55 ng/ml, Mann-Whitney test P = 0.03), von Willebrand factor (114 versus 96 IU/l; unpaired t-test P .ltoreq. 0.001) and fibrinogen (3.3 versus 2.9 g/l; unpaired t-test P .ltoreq. 0.001). There were significant correlations between fibrinogen and P-selectin (r = 0.16; P = 0.02) and von Willebrand factor (r = 0.39; P < 0.001), but not between P-selectin and von Willebrand factor. There were no differences in these factors between patients with (n = 53) and without (n = 51) antihypertensive therapy or between those with good blood pressure control (systolic/diastolic .ltoreq. 160/90 mmHg; n = 17) and those with poor control. A stepwise multiple regression analysis showed that diastolic blood pressure was a significant predictor for soluble P-selectin levels; diastolic blood pressure and von Willebrand factor levels were significant predictors for fibrinogen levels (P < 0.05). Conclusions: This study suggests that hypertensives have high plasma fibrinogen levels, platelet dysfunction (which could contribute to atherogenesis, as indicated by raised soluble P-selectin levels) and endothelial dysfunction (as indicated by high von Willebrand factor levels), which are related to diastolic blood pressure. These factors may act synergistically to increase atherogenesis and may explain the high risk of atherosclerotic vascular disease in hypertensives.

L66 ANSWER 11 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 2

1995:1000623 Shear-induced platelet aggregation in normal subjects and stroke patients. Konstantopoulos, Konstantinos; Grotta, James C.; Sills, Cynthia; Wu, Kenneth K.; Hellums, J. David (Cox Laboratory Biomedical Engineering, Rice University, Houston, Tex., TX, USA). Thromb. Haemostasis, 74(5), 1329-34 (English) 1995. CODEN: THHADQ. ISSN: 0340-6245.

AB Elevated levels of shear stress that occur in stenotic arteries may induce platelet aggregation and initiate thrombosis. Shear-induced platelet aggregation (SIPA) was studied in groups of ischemic stroke patients and normal subjects usign a viscometric-flow cytometric technique. Twenty-three patients who sustained an ischemic stroke that was not of cardiac origin were inlcuded in this study, and were classified either as **atherosclerotic** (n = 15) or as lacunar (n = 8) stoke patients. The results show that shear stresses at the levels which occur in arteries partially occluded by **atherosclerosis** or vascular spasm strongly activate and aggregate paltelets, and this response is much more pronounce din non-lacunar stroke patients who had documented **atherosclerotic** disease of their cerebral vessels. SIPa is not affected by the time of blood drawing after the onset of stoke suggesting that these platelet abnormalities are not transient but chronic. Furthermore, the extent of platelet activation detected by an anti-**P-selectin** monoclonal antibody and the proportion of neutrophil-platelet aggregates circulating in vivo are significantly higher in the **atherosclerotic** stroke patients studied at least one month after the onset of stroke. Thes results indicate that the enhanced platelet responses obsd. in **atherosclerotic** stroke patients are not conseqluences of ischemia, and therefore both platelet activation and elevated SIPA may be considered as important risk factors for stroke. The methodol. developed in this work may be useful for characterization of platelet resactivity, and may contribute to our understanding of thrombotic mechanisms.

L66 ANSWER 12 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 3
1995:720907 Document No. 123:195650 Blood cell dynamics in P-selectin-deficient mice. **Johnson, Robert C.**; Mayadas, Tanya N.; Frenette, Paul S.; Mebius, Reina E.; Subramaniam, Meera; Lacasce, Ann; Hynes, Richard O.; **Wagner, Denisa D.** (Brigham Women's Hospital, Harvard Medical School, Boston, MA, USA). Blood, 86(3), 1106-14 (English) 1995. CODEN: BLOOAW. ISSN: 0006-4971.

AB P-selectin is expressed on the surfaces of activated platelets and endothelium where it mediates binding to leukocytes. P-selectin-deficient mice were shown to exhibit peripheral neutrophilia (T. N. Mayades et al., 1993). The authors now show that this is not caused by changes in bone marrow precursors nor by a lack of neutrophil margination. Both P-selectin-pos. and -neg. animals displayed similar increases in peripheral blood neutrophil nos. after injection of epinephrine. However, clearance of 51chromium-labeled neutrophils is delayed in mice deficient for P-selectin, indicating that the neutrophilia is at least in part the result of delayed removal. The authors detected no obvious alterations in lymphocyte differentiation, distribution, or adhesion to high endothelial venules in peripheral lymph nodes. Through intravital microscopy, the authors examd. the impact of P-selectin deficiency on leukocyte/endothelial interaction beyond the initial stages of inflammation. Four hours after the administration of an inflammatory irritant, leukocyte rolling was obsd. even in the absence of P-selectin. There were significantly fewer rolling cells relative to wild-type mice, and their velocity was reduced. Moreover, in the peritonitis model, the no. of peritoneal macrophages in wild-type mice increased threefold at 48 h, whereas the macrophages in the mutant mice remained near baseline levels. Thus, whereas P-selectin is known to be involved in early stages of an inflammatory response, the results indicate that it is addnl. responsible for leukocyte rolling and macrophage recruitment in more prolonged tissue injury.

L66 ANSWER 13 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 4
1995:796973 Document No. 123:195640 von Willebrand factor, soluble **P-selectin**, tissue plasminogen activator and plasminogen activator inhibitor in **atherosclerosis**. Blann, A. D.; Dobrotova, M.; Kubisz, P.; McCollum, C. N. (Dep. Surgery, Univ. Hospital South Manchester, Manchester, UK). Thromb. Haemostasis, 74(2), 626-30 (English) 1995. CODEN: THHADQ. ISSN: 0340-6245.

AB Tissue plasminogen activator antigen (tPA), plasminogen activator inhibitor antigen (PAI-1), sol. **P-selectin** and von Willebrand factor antigen (vWf) were measured by ELISA in 41 patients with peripheral vascular disease (PVD), 41 with ischemic heart disease (IHD) and in 46 age and sex matched asymptomatic controls. Increased vWf was found in patients with IHD ($p = 0.0002$) and in patients with PVD ($p = 0.0011$) relative to the controls but levels did not differ between the two patient groups. Raised tPA found in both PVD ($p = 0.0006$) and IHD ($p = 0.0061$) compared to the controls also failed to differentiate the two groups of patients. Sol. **P-selectin** was also raised in both groups ($p = 0.003$ in IHD and $p = 0.0102$ in PVD) with no difference between the groups. There were no differences in levels of PAI-1 between the groups. In the subjects taken as a whole, there were significant Spearman's correlations between tPA and vWf ($r = 0.37$, $p < 0.001$), tPA and triglycerides ($r = 0.38$, $p < 0.001$), tPA and **P-selectin** ($r = 0.19$, $p = 0.032$), vWf and age ($r = 0.25$, $p = 0.005$) and inversely between vWf and HDL ($r = -0.25$, $p = 0.006$). These data support the concept that increased levels of tPA may be important in **atherosclerosis**, and indicate that sol. **P-selectin** may be useful in further anal. of the role of platelets and the endothelial cell in this disease.

L66 ANSWER 14 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1995:983949 Document No. 124:81189 Evaluation of platelet function by flow cytometric measurement of ligand binding. Bunescu, A.;

Lundahl, J.; Soederstroem, T.; Lindahl, T.; Larsson, A.; Egberg, N. (Dep. Clinical Chem. Blood Coagulation, Karolinska Hosp., Stockholm, S-171 76, Swed.). Platelets, 6(6), 340-5 (English) 1995. CODEN: PLTEEF. ISSN: 0953-7104.

AB Rapid and relevant evaluation of platelet function is often clin. important. By fluorescent labeled chicken antibodies (which do not bind to Fc-receptors) against fibrinogen and von Willebrand factor and flow cytometry, the authors have detd. the time course of ligand assocn. to platelets after stimulation with ADP and ristocetin resp. The expression of guanosine 5'-phosphate (**GMP**)-**140** was also measured. The authors have applied this technique to evaluate platelet function during platelet storage and cardiopulmonary bypass. There was a significant redn. of the binding of fibrinogen and von Willebrand factor and significantly increased expression of **GMP-140** after 9 days of storage. Changes in metabolic variables such as lactate accumulation, glucose consumption and decrease in pH confirm that the functional impairment is due to a large extent to a deteriorated platelet metab. No significant differences were found between samples taken before and during cardiopulmonary bypass, but there was a tendency towards increased ligand binding as well as increased expression of **GMP-140** at the end of cardiopulmonary bypass. The flow cytometric technique that is described may be useful for evaluation of platelet function and platelet activation in vivo.

L66 ANSWER 15 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 5

1995:683383 Document No. 123:166534 Platelet-derived microparticles may influence the development of **atherosclerosis** in diabetes mellitus. Nomura, Shosaku; Suzuki, Masahiko; Katsura, Kaoruko; Xie, Gui Lan; Miyazaki, Yasuhiko; Miyake, Tetsuya; Kido, Hirofumi; Kagawa, Hideo; Fukuhara, Shirou (The First Department of Internal Medicine, Kansai Medical University, 10-15, Fumizono-cho, Moriguchi, Osaka, 570, Japan). Atherosclerosis (Shannon, Irel.), 116(2), 235-40 (English) 1995. CODEN: ATHSBL. ISSN: 0021-9150.

AB The authors investigated the assocn. between low-d. lipoprotein (LDL), triglycerides, and platelet activation in 18 patients with hypertension age 41-64 yr and 18 with diabetes mellitus aged 43-70 yr. Platelet **P-selectin** positivity and microparticle level (indicators of activation) were both significantly higher in the diabetics than in healthy controls (**P-selectin**: 28.0% vs. 7.3%,; microparticles: 1900 vs. 526/104 platelets). In contrast, there was no significant increase of either parameter in the patients with hypertension. Plasma microparticle levels were also significantly greater in the diabetics with high LDL levels than in those with low LDL levels (2375 vs. 1519/104 platelets), and in those with high rather than low triglyceride levels (2188 vs. 1492/104 platelets). However, platelet positivity for **P-selectin** was not significantly different between these two subgroups. Microparticle and **P-selectin** levels both showed no significant difference between the hypertensive patients with high and low LDL or triglyceride levels. These results suggest that platelet-derived microparticles may participate in the development or progression of **atherosclerosis** in patients with diabetes mellitus.

L66 ANSWER 16 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1996:112331 Evidence for thrombin-induced human platelet secretion regulated by the cytoskeleton. Dai, Yun; Li, Jin (Dep. Histol. Embryol., Military Med. Coll., Canton, Peop. Rep. China, 510515, Peop. Rep. China). Shiyan Shengwu Xuebao, 28(3), 235-40 (English) 1995. CODEN: SYSWAE. ISSN: 0001-5334.

AB Human blood platelets store an abundance of growth factors, adhensive proteins, coagulation factors, platelet-specific proteins, calcium, serotonin, and adenine nucleotides in their secretory organelles. After exposure to stimuli (thrombin, collagen, ADP, etc.), the platelets undergo a rapid series of morphol. change from characteristic disks to spheres with several filopodia, adhension to the inner surface of blood vessels, and aggregation among the

platelets. Most of these changes are usually accompanied by secretion or release of dense bodies (release I) and .alpha.-granules (release II). The secreted products play essential parts in a variety of important physiol. and/or pathol. events, such as hematosis, thrombosis, blood coagulation, inflammation, and **atherosclerosis**. Little is known, however, for regulatory mechanism of platelet secretion. Platelets are a distinct kind of cells with many special organelles, but without a nucleus. It also contains a large amt. of cytoskeleton. The numerous investigators have suggested that the platelet responses to stimuli are intimately linked to events involving cytoskeleton within the platelets. During platelet activation, as revealed by electron microscopy, the secretory organelles become centralized and enveloped by circular microtubules and a filamentous network. It is implied a possible relationship between cytoskeleton and platelet secretion. However, the precise role of cytoskeleton in platelet secretion remains uncertain. By using exposed **GMP-140** (a platelet granule-membrane protein with MW of 140 kDa) as a specific signal of secretion, the present study was designed to investigate the effects of microtubular and microfilamental inhibitors on thrombin-induced platelet secretion.

L66 ANSWER 17 OF 61 MEDLINE DUPLICATE 6
95209187 Endothelial heterogeneity and intimal blood-borne cells. Relation to human atherosclerosis. Romanov Y A; Balyasnikova I V; Bystrevskaya V B; Byzova T V; Ilyinskaya O P; Krushinsky A V; Latsis R V; Soboleva E L; Tararak E M; Smirnov V N. (Institute of Experimental Cardiology, Russian Academy of Medical Sciences, Moscow..)ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, (1995 Jan 17) 748 12-37; discussion 37-9. Journal code: 5NM. ISSN: 0077-8923. Pub. country: United States. Language: English.

L66 ANSWER 18 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1996:100010 **P-selectin** knockout: a mouse model for various human diseases. Wagner, Denisa D. (Center for Blood Research, Harvard Medical School, Boston, MA, 02115, USA). Ciba Found. Symp., Volume Date 1995, 189, 2-16 (English) 1995. CODEN: CIBSB4. ISSN: 0300-5208.
AB **P-selectin** is a transmembrane adhesion receptor specific to platelets and endothelial cells. It has an N-terminal lectin domain that recognizes specific carbohydrate moieties on monocytes, neutrophils and some other subsets of leukocytes. **P-selectin** is stored in granules and is expressed on the plasma membrane only after the cells are stimulated by vascular injury or during inflammation. Physiol. **P-selectin** is likely to be involved in the recruitment of leukocytes that promote wound healing and fight infection. There are many disorders in which the excessive recruitment of leukocytes is characteristic, including chronic inflammation, **atherosclerosis**, arthritis, diabetes, asthma and reperfusion injury. Because certain cancer cells also express the ligand for **P-selectin** it is possible that this receptor is involved in metastasis. To study the specific role of **P-selectin** in these pathol. processes, we have prepd. a mouse lacking **P-selectin** through gene targeting. Leukocyte interaction with the vessel wall is defective in these animals as leukocytes do not roll in the mesenteric venules and their extravasation at sites of inflammation and vessel injury is limited. We are testing these animals in models of the various diseases mentioned above in order to evaluate when the absence of **P-selectin** is beneficial.

rcg 2-27

L66 ANSWER 19 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1994:570544 Document No. 121:170544 Method for inhibition of cell adhesion to receptors containing selectins. Carson, Dennis A.; Wicks, Ian (Reagents of the University of California, USA). PCT Int. Appl. WO 9414472 A1 940707, 42 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 93-US12464

931221. PRIORITY: US 92-994650 921222.

AB A method for inhibition of adhesion of cells to receptors contg. selectins in mammals is disclosed whereby an anti-adhesion enzyme is administered to the mammal in a therapeutically effective dosage. In a preferred embodiment, the anti-adhesion enzyme will be administered to treat a chronic or acute inflammatory condition (preferably the latter). In this context, the therapeutically effective dosage will be a dosage sufficient to achieve detectable redn. of the inflammation without substantial toxicity. The enzyme administered will specifically cleave carbohydrate residues which are involved in forming bonds between carbohydrate residues in ligands (typically on leukocytes) which are specific for selectin-contg. receptors (typically on endothelial cells), in particular, bonds formed by fucosylated and/or sialylated residues. The enzyme will preferably be a fucosidase or sialidase and is preferably used in recombinant form. Means are also described whereby the activity of the enzyme can be enhanced to perform optimally at pH 7-7.4 (i.e., the pH of plasma). The enzyme may also be modified to extend its in vivo half-life and shelf life. It is expected that the same enzyme will cleave many adhesion residues. Sialidase of Clostridium prevented neutrophil entry into lung tissue in an adult respiratory distress syndrome rat model.

L66 ANSWER 20 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:555760 Document No. 121:155760 Glycoprotein ligand for **P-selectin** and methods of use thereof. Cummings, Richard D.; Moore, Kevin L.; Mcever, Rodger P. (University of Oklahoma, USA). PCT Int. Appl. WO 9411498 A1 940526, 65 pp. DESIGNATED STATES: W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 93-US11129 931116. PRIORITY: US 92-976552 921116.

AB **P-selectin** has been demonstrated to bind primarily to a single glycoprotein ligand on neutrophils and HL-60 cells, when assessed by blotting assays and by affinity chromatog. of [3H]glucosamine-labeled HL-60 cell exts. on immobilized **P-selectin**. This mol. was characterized and distinguished from other well-characterized neutrophil membrane proteins with similar apparent mol. mass. The purified ligand, or fragments thereof, including both the carbohydrate and protein components, or antibodies to the ligand, or fragments or components thereof, can be used as inhibitors of binding of **P-selectin** to cells. The **P-selectin** ligand and antibody to the ligand or polypeptide of the ligand are useful for modulating inflammatory or hemostatic response, or for inhibiting tumor metastasis.

L66 ANSWER 21 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:315824 Document No. 120:315824 **P-selectin**-derived inhibitors of leukocyte adhesion. Heavner, George A.; Epps, Leon A. (Centocor, Inc., USA). PCT Int. Appl. WO 9405314 A1 940317, 56 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 93-US7964 930824. PRIORITY: US 92-941652 920908.

AB Novel peptides derived from amino acids 42-48 of **P-selectin** are characterized for diagnostic and pharmaceutical use in the control of leukocyte adhesion. Peptides were synthesized by Fmoc chem. and tested for their ability to inhibit the binding of **P-selectin** by neutrophils. Inhibition of binding by 0.3 .mu.M peptide was in the range 11-100%.

L66 ANSWER 22 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:426895 Document No. 121:26895 Cyclic peptide inhibitors of cellular adhesion derived from selectins. Heavner, George A. (Centocor, Inc., USA). PCT Int. Appl. WO 9405310 A1 940317, 175 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2.

APPLICATION: WO 93-US8504 930908. PRIORITY: US 92-941653 920908.

AB Novel cyclic peptides derived from a conserved sequence in selectins are biol. active and useful as pharmaceuticals. Specific points of cyclization or conformational restriction in conjunction with specific substitutions have been identified that not only unexpectedly increase the biol. activity of these compds., but also significantly increase their resistance to enzymic degrdn. Formulas of the active compds. and representative examples of preferred peptides are presented.

L66 ANSWER 23 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:290096 Document No. 120:290096 Selectin-dependent adhesion-inhibiting peptides for treating inflammation, ischemia, etc.. Heavner, George A.; Kruszynski, Marian; Falcone, Margaret L. (Centocor, Inc., USA). PCT Int. Appl. WO 9405269 A1 940317, 39 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 93-US8436 930908. PRIORITY: US 92-941649 920908.

AB The present invention provides six peptides having as their core region portions of the 11-18 amino acid sequence of **P-selectin**, E-selectin or L-selectin. The invention also provides pharmaceutical compns. comprising the peptides of the invention, and diagnostic and therapeutic methods utilizing the peptides and pharmaceutical compns. of the invention. The peptides are useful for redn. of inflammation or coagulation, for inhibition of leukocyte adhesion, or for treatment of inflammation, ischemia, reperfusion, bacterial sepsis, disseminated intravascular coagulation, adult respiratory distress syndrome, tumor metastasis, rheumatoid arthritis, and **atherosclerosis**.

L66 ANSWER 24 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:105012 Document No. 120:105012 Blocking intercellular interactions with CD43 chimeric molecules. Ardman, Blair (New England Medical Center Hospitals, Inc., USA). PCT Int. Appl. WO 9400143 A1 940106, 36 pp. DESIGNATED STATES: W: JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 93-US4517 930513. PRIORITY: US 92-891571 920601.

AB Interaction between a 1st and a 2nd cell in a mammal is inhibited by administering a sol. chimeric mol. which includes: (a) a cell targeting mol. which is capable of specifically recognizing and binding to a mol. on the surface of the 1st cell covalently bonded to (b) a CD43 extracellular domain bearing a net neg. charge at physiol. pH. CD43 protein interferes with intercellular adhesion, as illustrated by the relative lack of LFA-1-mediated adhesion of T-cells to CD43-expressing HeLa cell transfectants compared to normal HeLa cells. This effect of CD43 was prevented by incubation with neuraminidase, which removed neg. charged sialic acid residues. Examples of cell targeting mols. are: (1) a P-selecting-binding portion of an LNF III receptor protein; (2) an ELAM-1-binding portion of a sialyl Lewisx receptor protein; (3) a VLA-4-binding portion of a VCAM-1 receptor protein; (4) a HIV-binding portion of CD4; (5) an LFA-1-binding, rhinovirus-binding, or Plasmodium-binding portion of an ICAM-1 receptor protein.

L66 ANSWER 25 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1995:210446 Document No. 122:6189 Isolation and Characterization of Natural Protein-Associated Carbohydrate Ligands for E-Selectin. Patel, Thakor P.; Goelz, Susan E.; Lobb, Roy R.; Parekh, Raj B. (Oxford GlycoSystems, Blacklands Way/ Abingdon/ Oxon, OX14 1RG, UK). Biochemistry, 33(49), 14815-24 (English) 1994. CODEN: BICHAW. ISSN: 0006-2960. OTHER SOURCES: CJACS-IMAGE; CJACS.

AB A comparative anal. of carbohydrate 'libraries' derived from cell lines binding E-selectin with differing avidity identified probable endogenous protein-assocd. carbohydrate ligand candidates for E-selectin. Three unusual structures, which constitute less than 3% of cell surface protein-assocd. carbohydrate, were unique to the E-selectin-binding cells, including neutrophils and the monocytic cell line U937. All are tetraantennary N-linked structures with a

NeuAc.alpha.2.fwdarw.3Gal.beta.1.fwdarw.4(Fuc.alpha.1.fwdarw.3)GlcNA c.beta.1.fwdarw.3Gal.beta.1.fwdarw.4(Fuc.alpha.1.fwdarw.3)GlcNAc lactosaminoglycan extension (diSLex) on the arm linked through the C4 residue on the mannose. While all contained the expected SLex [NeuAc.alpha.2.fwdarw.3Gal.beta.1.fwdarw.4(Fuc.alpha.1.fwdarw.3)GlcN Ac] moiety, these structures have an addnl. fucosylated lactosamine unit. Direct evidence that these diSLex-contg. structures are, indeed, high-affinity ligands for E-selectin came from the use of recombinant sol. E-selectin-agarose affinity chromatog. It was found that these three carbohydrate structures bound specifically to the E-selectin column. SLex itself does not bind under identical conditions. In summary, these related structures: (1) all possess an unusual 3-sialyl di-Lewis x extension on one arm of an N-linked tetraantennary glycan; (2) of the cells tested, are present only on E-selectin-binding leukocytes and leukocytic cell lines; (3) bind to E-selectin with a relatively high affinity (Kd < .mu.M) and one greater than that of 3-sialyl Lewis x or 3-sialyl Lewis a; and (4) represent a very small percentage of the protein-assocd. carbohydrate. These carbohydrate structures appear to be present on only a very small no. of cell surface proteins and may alone be responsible for the specificity of E-selectin-dependent adhesion.

L66 ANSWER 26 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1994:530632 Document No. 121:130632 Selectin ligands. Varki, Ajit (Glycobiology Program, Divison of Cellular and Molecular Medicine, La Jolla, CA, 92093, USA). Proc. Natl. Acad. Sci. U. S. A., 91(16), 7390-7 (English) 1994. CODEN: PNASA6. ISSN: 0027-8424.
AB A review, with 132 refs., on selectins and their carbohydrate ligands. The biol. relevant selectin ligands are diverse and complex macromols. that share in common certain types of anionic carbohydrate structures. High affinity recognition of seemingly disparate oligosaccharides may involve the formation of similar clustered saccharide patches.

new 2-27

L66 ANSWER 27 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 7
1994:671916 Document No. 121:271916 Platelet .alpha.-granule release in cocaine users. Rinder, Henry M.; Ault, Kenneth A.; Jatlow, Peter I.; Kosten, Thomas R.; Smith, Brian R. (School of Medicine, Yale Univ., New Haven, CT, USA). Circulation, 90(3), 1162-7 (English) 1994. CODEN: CIRCAZ. ISSN: 0009-7322.
AB Cocaine use has been assocd. with arterial occlusion resulting from platelet-rich thrombi and with an accelerated, often atypical **atherosclerotic** lesion that could be ascribed to platelet activation and platelet .alpha.-granule release. Using a flow cytometric method to quantitate the percent of circulating activated platelets in whole blood (those that express the .alpha.-granule membrane protein **P-selectin**), we found that 5 of 25 samples from 12 long-term cocaine users had a baseline level of circulating activated platelets > 3 SD (range, 19% to 60%) above the mean (4.4 .+-. 3.7%, mean .+-. 1 SD) for 85 nonusers (sample n = 130). This subset resulted in a significantly higher mean baseline level of circulating activated platelets (11.8 .+-. 14.4%) for all cocaine users (P = 0.1). By contrast, cocaine and its metabolites, at concns. documented as obtainable during in vivo cocaine use (10-7 to 10-5 mol/L), had no effect on in vitro platelet activation or aggregation, either directly or in concert with platelet agonists. However, in expts. in which cocaine users received blinded infusions of placebo or cocaine, the mean percent of circulating activated platelets rose significantly (P <0.5) after infusion of either placebo (peak 77 .+-. 31%) or cocaine (Peak 65 .+-. 28%), the latter at doses resulting in peak plasma cocaine levels averaging <10-6 mol/L. Long-term cocaine use in some subjects is intermittently assocd. with high basal levels of circulating platelets that have undergone .alpha.-granule release. The inability of cocaine and its metabolites at concns. of 10-7 to 10-5 mol/L to cause platelet **P-selectin** expression in vitro in this study, coupled with the acute increase in circulating activated platelets obsd. in vivo after either cocaine or placebo infusion, suggests that in vivo platelet .alpha.-granule release assocd. with cocaine

use may occur through indirect rather than direct effects of the drug.

L66 ANSWER 28 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 8
1994:531338 Document No. 121:131338 Increase in the adhesion molecule **P-selectin** in endothelium overlying **atherosclerotic** plaques: Coexpression with intercellular adhesion molecule-1. Johnson-Tidey, Ruth R.; McGregor, John L.; Taylor, Peter R.; Poston, Robin N. (Dep. Exp. Pathol., UMDS, London, UK). Am. J. Pathol., 144(5), 952-61 (English) 1994. CODEN: AJPAA4. ISSN: 0002-9440.

AB **P-selectin** (**GMP-140**) is an adhesion mol. present within endothelial cells that is rapidly translocated to the cell membrane upon activation, where it mediates endothelial-leukocyte interactions. Immunohistochem. anal. of human **atherosclerotic** plaques has shown strong expression of **P-selectin** by the endothelium overlying active **atherosclerotic** plaques. **P-selectin** is not, however, detected in normal arterial endothelium or in endothelium overlying inactive fibrous plaques. Color image anal. was used to quantitate the degree of **P-selectin** expression in the endothelium and demonstrates a statistically significant increase in **P-selectin** expression by **atherosclerotic** endothelial cells. Double immunofluorescence shows that some of this **P-selectin** is expressed on the luminal surface of the endothelial cells. Previous work has demonstrated a significant up-regulation in the expression of the intercellular adhesion mol.-1 in **atherosclerotic** endothelium and a study on the expression of intercellular adhesion mol.-1 and **P-selectin** in **atherosclerosis** shows a highly pos. correlation. These results suggest that the selective and cooperative expression of **P-selectin** and intercellular adhesion mol.-1 may be involved in the recruitment of monocytes into sites of **atherosclerosis**.

rej 2-27

L66 ANSWER 29 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
94310893 EMBASE P-selectin mediates the interaction of circulating leukocytes with platelets and microvascular endothelium in response to oxidized lipoprotein in vivo. Lehr H.-A.; Olofsson A.M.; Carew T.E.; Vajkoczy P.; Von Andrian U.H.; Hubner C.; Berndt M.C.; Steinberg D.; Messmer K.; Arfors K.E.. Department of Pathology, Univ. of Washington Medical Center, 1959 NE Pacific St., Seattle, WA 98195, United States. LAB. INVEST. 71/3 (380-386) 1994. ISSN: 0023-6837. CODEN: LAINAW. Pub. Country: United States. Language: English. Summary Language: English.

AB BACKGROUND: Oxidized low density lipoprotein (oxLDL) has been demonstrated to stimulate leukocyte/endothelium interaction, an early feature of atherogenesis. Using the skinfold chamber model for intravital microscopy in hamsters and mice, we have shown that oxLDL-induced leukocyte adhesion to microvascular endothelium shares many characteristics with leukocyte adhesion during inflammation and ischemia/reperfusion, including the involvement of .beta.2 integrin adhesion molecules. In light of the two-step model of leukocyte adhesion, we have examined the contribution of P-selectin to oxLDL-induced leukocyte/endothelium interaction. P-selectin is an inducible adhesion molecule on platelets and endothelium, mediating the initial steps of leukocyte margination and rolling along the endothelial lining, as well as of aggregate formation between platelets and leukocytes. EXPERIMENTAL DESIGN: For our studies, we used the dorsal skinfold chamber model for intravital fluorescence microscopy on awake Syrian golden hamsters. Hamsters were treated 10 minutes before oxLDL-injection (oxidized by Cu2+, 4 mg/kg body weight, intravenously) with blocking antibodies to P-selectin (2 mg/kg body weight intravenously, N = 7). RESULTS: In seven control animals (pretreated with an irrelevant IgG antibody), oxLDL injection elicited leukocyte rolling and adhesion on both venular and arteriolar endothelium, and also the formation of aggregates tumbling down the microvessels and firmly adhering to the

microvascular endothelium. The aggregates consisted of leukocytes and activated, dendritic platelets, as assessed by scanning electron microscopy of the buffy coat isolated by density gradient centrifugation of whole blood taken from hamsters 15 minutes after injection of oxLDL. Leukocyte adhesion to venular and arteriolar endothelium, as well as the formation of leukocyte/platelet aggregates were significantly reduced by pretreatment of the animals with anti-P-selectin antibodies. CONCLUSIONS: These data emphasize the similarities between leukocyte adhesion in response to oxLDL and in other pathophysiologic conditions, identifying P-selectin as a crucial player in the interaction between leukocytes and microvascular endothelium as well as in the formation of circulating leukocyte/platelet aggregates.

L66 ANSWER 30 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1995:839479 Document No. 123:310911 Endothelium, blood-born cells and intimal colony forming units in human atherogenesis. Balyasnikova, I. V.; Byzova, T. V.; Bystrevskaya, V. B.; Ilyinskaya, O. P.; Krushinsky, A. V.; Popkova, V. M.; Romanov, Yu. A.; Soboleva, E. L.; Tararak, E. M.; Smirnov, V. N. (Cardiology Research Center, Academy Medical Sciences, Moscow, Russia). Eur. Sect. Meet., Int. Soc. Heart Res., 15th, 327-30. Editor(s): Haunsoe, Stig; Kjeldsen, Keld. Monduzzi Editore: Bologna, Italy. (English) 1994. CODEN: 61SCA9.
AB Human large vessel endothelium in situ is morphol. heterogeneous due to the presence of large and multinucleated endothelial cells (ECs). In cell culture, significant differences in adhesive properties and variations in distribution of adhesion proteins (**GMP-140**, ICAM-1) were found even in neighboring cells forming polymorphous endothelial monolayer. This finding may explain the appearance of subendothelial clusters consisting of blood cells in aortic regions in situ covered predominantly by giant ECs. Some of these clusters contained low-differentiated precursor cells giving rise to hematopoietic- or stromal-type colonies in specific culture conditions. It is proposed that the foci of ectopic hemato- and stromapoiesis in subendothelial intima can affect normal metabolic parameters in the vessel wall and partly explain the localization patterns of **atherosclerotic** lesions.

L66 ANSWER 31 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
94319778 EMBASE Thrombosis and inflammation as multicellular processes: Significance of cell-cell interactions. Marcus A.J.. Hematology and Oncology, Department of VA Medical Center, 423 East 23rd St, New York, NY 10010, United States. SEMIN. HEMATOL. 31/4 (261-269) 1994. ISSN: 0037-1963. CODEN: SEHEA3. Pub. Country: United States. Language: English.

L66 ANSWER 32 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1994:628754 Document No. 121:228754 Biological significance of L-selectin (LECAM-1) and its ligand. Miyasaka, Masayuki; Tamatani, Takuya; Kawashima, Hiroto (Department of Immunology, Tokyo Metropolitan Institute of Medical Science, Tokyo, 113, Japan). Int. Congr. Ser. - Excerpta Med., 1051(Endothelium-Derived Factors and Vascular Functions), 249-52 (English) 1994. CODEN: EXMDA4. ISSN: 0531-5131.
AB L-selectin (LECAM-1) is a leukocyte adhesion mol. for endothelium and plays an important role in leukocyte rolling along activated endothelium. The authors have obtained cDNA encoding rat L-selectin and generated a sol. fusion protein of rat L-selectin and human IgG Fc portion (rLEC-Ig). They then used this protein to characterize the ligands in terms of their biochem. and tissue distribution. Here the authors show the heterogeneity of the L-selectin ligands and also discuss the possible significance of L-selectin/ligands interaction.

L66 ANSWER 33 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1994:295629 Document No. 120:295629 The protective role of high-density lipoprotein on oxidized-low-density-lipoprotein-induced U937/endothelial cell interactions. Maier, Jeanette Anne Marie; Barenghi, Livia; Pagani, Franco; Bradamante, Silvia; Comi, Paola;

Ragnotti, Giovanni (Dep. Biomed. Sci. Technol., Osp. San Raffaele, Milan, Italy). Eur. J. Biochem., 221(1), 35-41 (English) 1994. CODEN: EJBCAI. ISSN: 0014-2956.

AB The adherence of monocytes to the endothelium is an early event in atherogenesis. The authors have investigated this process by examg. whether native and oxidized low-d. and high-d. lipoproteins could modulate this process. Only oxidized low-d. lipoprotein caused a significant dose-dependent and time-dependent increase in U937 monocyte-like cell line binding to human endothelial cells, by a process which required de novo protein synthesis. Interestingly, E-selectin, intercellular adhesion mol.-1, vascular cell-adhesion mol. or **P-selectin** induction was not apparent in this system suggesting the presence of an alternative system for the interaction of endothelial cells with monocyte-like cells in response to oxidized low-d. lipoprotein. High-d. lipoprotein completely suppressed oxidized low-d.-lipoprotein-induced adhesion of U937 cells to the endothelial monolayer, while oxidized high-d. lipoprotein did not. These data suggest that the balance between native and oxidized lipoproteins may play a role in the formation of the **atherosclerotic** lesion by modulating monocyte endothelial interactions.

L66 ANSWER 34 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:674482 Document No. 121:274482 L-selectin and the ligand molecules. Imai, Yasuyuki (Fac. Pharm. Sci., Univ. Tokyo, Tokyo, 113, Japan). Immunol. Front., 4(1), 25-31 (Japanese) 1994. CODEN: IMFREG. ISSN: 0917-0774.

AB A review with 28 refs. on L-selectin, a lectin-like leukocyte adhesion protein and the ligand mols. in lymphocytes.

L66 ANSWER 35 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1994:647746 Document No. 121:247746 A Plasmodium falciparum isolate with a chromosome 9 deletion expresses a trypsin-resistant cytoadherence molecule. Chaiyaroj, Sansanee C.; Coppel, Ross L.; Magowan, Cathleen; Brown, Graham V. (The Walter and Eliza Hall Institute of Medical Research, Post Office Royal Melbourne Hospital, Victoria, 3050, Australia). Mol. Biochem. Parasitol., 67(1), 21-30 (English) 1994. CODEN: MBIPDP. ISSN: 0166-6851.

AB Sequestration of Plasmodium falciparum infected erythrocytes in the cerebral circulation is strongly implicated in the pathogenesis of cerebral malaria. From previous studies it was postulated that genes essential for cytoadherence were located on the right arm of chromosome 9 as P. falciparum isolates with a deletion in this region lost the capacity to cytoadhere in vitro and no longer expressed Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP-1) on the surface of the infected cells. The authors have selected a P. falciparum isolate from Papua New Guinea for high levels of cytoadherence to human umbilical vein endothelial cells (HUVECs) and have shown that the cloned parasite has several novel properties related to cytoadherence. The cloned parasite adheres to HUVECs, does not bind to melanoma cells, and expresses a surface mol. with most of the properties of PfEMP-1, despite a deletion in the right arm of chromosome 9. Interestingly, the surface expressed PfEMP-1 in this strain is resistant to trypsin treatment and infected cells continue to cytoadhere after trypsin digestion at a concn. of 100 .mu.g mL-1. The receptor on HUVECs for the cloned parasite lines is a mol. different from any previously described, as parasitized cells do not adhere to sol. intercellular adhesion mol. 1, thrombospondin, vascular cell adhesion mol. 1, E-selectin or **P-selectin**, nor to CD36. This work, taken together with the results from previous studies, suggests that the ability of parasites to cytoadhere is encoded in at least two distinct genomic locations in the parasite, and the diversity of receptor-ligand interaction is greater than previously described.

L66 ANSWER 36 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1993:531547 Document No. 119:131547 Method for inhibiting selectin-dependent adhesion of leukocytes and platelets by O-glycosylation modification. Kojima, Naoya; Handa, Kazuko;

Hakomori, Senitiroh (Biomembrane Institute, USA). PCT Int. Appl. WO 9311776 A1 930624, 27 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 92-US10181 921201. PRIORITY: US 91-805949 911212.

AB O-glycosylation and O-glycosylation extension inhibitors influence selectin-dependent interactions between cells and between cells and platelets. A therapeutic contg. the O-glycosylation inhibitor or O-glycosylation extension inhibitor is claimed. The inhibitor is e.g. benzyl-.alpha.-N-acetylgalactosamine (I). Culturing of HL60 cells with I (2mM) resulted in complete or nearly complete blocking of expression of sialosyl-Lex; in contrast, reagents affecting N-glycosylation had no inhibitory effect on sialosyl-Lex expression. Cells treated with I showed clear inhibition of adhesion to stimulated human umbilical vein endothelial cells.

L66 ANSWER 37 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1993:426686 Document No. 119:26686 Inhibition of vascular narrowing using anti-**PADGEM** antibodies. Palabrica, Theresa M.; Furie, Bruce E.; Furie, Barbara C. (Biogen, Inc., USA; New England Medical Center Hospitals, Inc.). PCT Int. Appl. WO 9306863 A1 930415, 32 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 92-US8163 920930. PRIORITY: US 91-768834 910930.

AB After treatment of occlusive artery disease, e.g. by angioplasty, endarterectomy, atherectomy, etc., vascular narrowing (e.g. restenosis or thrombosis) is prevented by administration of a (monoclonal, recombinant, chimeric, and/or humanized) antibody (fragment) to platelet activation-dependent granule-external membrane (**PADGEM**) protein. Thus, mouse monoclonal antibody GA6 to **PADGEM** from human platelets inhibited vascular narrowing in a thrombogenic Dacron arteriovenous shunt model in baboons.

L66 ANSWER 38 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1993:470376 Document No. 119:70376 Leukocyte adhesion molecule-1 (LAM-1) and ligand thereof and diagnostic and therapeutic uses thereof. Tedder, Thomas F.; Spertini, Olivier G. (Dana-Farber Cancer Institute, Inc., USA). PCT Int. Appl. WO 9306835 A1 930415, 46 pp. DESIGNATED STATES: W: AU, CA, JP. (English). CODEN: PIXXD2. APPLICATION: WO 92-US8467 921005. PRIORITY: US 91-770608 911003.

AB LAM-1, a leukocyte-assocd. cell surface protein, is characterized; it contains domains homologous with binding domains of animal lectins, growth factors, and C3/C4 binding proteins. CDNA and genomic sequences are presented. Also disclosed are methods and agents for detecting, identifying, and characterizing the LAM-1 ligand. The LAM-1 protein, a ligand-binding fragment thereof, or an antagonist to the LAM-1 protein or ligand-binding fragment are used in methods of detecting sites of inflammation or disease in a human patient. They are also used in therapeutic compns. in methods of treating a patient suffering from a leukocyte-mobilizing condition. CDNA encoding LAM-1 was isolated from a human tonsil cDNA library and identified and characterized.

L66 ANSWER 39 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1993:186147 Document No. 118:186147 Interaction of **P-selectin** (CD62) and its cellular ligand: Analysis of critical residues. Hollenbaugh, Diane; Bajorath, Jurgen; Stenkamp, Ronald; Aruffo, Alejandro (Bristol-Myers Squibb Pharm. Res. Inst., Seattle, WA, 98121, USA). Biochemistry, 32(12), 2960-6 (English) 1993. CODEN: BICHAW. ISSN: 0006-2960. OTHER SOURCES: CJACS-IMAGE; CJACS.

AB **P-selectin** (CD62, **PADGEM**, **GMP140**) is a membrane glycoprotein which is rapidly mobilized to the surface of activated platelets and endothelial

cells where it mediates leukocyte-platelet and leukocyte-vascular endothelial cell adhesion, resp. **P-selectin** is a member of a family of adhesion mols. which includes the endothelial cell adhesion mol. E-selectin and the leukocyte adhesion mol. L-selectin. Selectins mediate cell-cell binding resulting from the interaction between the amino terminal lectin domains of the selectins and their resp. carbohydrate ligands. Here a three-dimensional model of the lectin domain of **P-selectin** is reported which was derived on the basis of its structural homol. to the rat mannose binding protein (MBP) whose crystal structure has recently been reported. On the basis of the model, a no. of point mutants were prepd. to identify the **P-selectin** binding site. The residues found to be important for binding are located in a shallow groove on the surface of the mol. composed of residues from the .beta.-2, -3, and -5 strands of the **P-selectin** lectin domain. A no. of residues within this groove, which are conserved among all selectins, were found to be crit. for **P-selectin** binding. They include Lys113, Tyr48, and Tyr94. The single substitutions Lys113Ala, Tyr48Ala, Tyr48Phe, Tyr94Ala, and Tyr94Phe abolished **P-selectin** binding to myeloid cells.

L66 ANSWER 40 OF 61 HCAPLUS COPYRIGHT 1996 ACS DUPLICATE 9
1993:601140 Document No. 119:201140 Leukocyte rolling and extravasation are severely compromised in P selectin-deficient mice. Mayadas, Tanya N.; **Johnson, Robert C.**; Rayburn, Helen; Hynes, Richard O.; **Wagner, Denisa D.** (New England Med. Cent., Tufts Univ., Boston, MA, 02111, USA). Cell (Cambridge, Mass.), 74(3), 541-54 (English) 1993. CODEN: CELLB5. ISSN: 0092-8674.

AB P selectin, expressed on surfaces of activated endothelial cells and platelets, is an adhesion receptor for leukocytes. The authors report that P selectin-deficient mice, generated by gene targeting in embryonic stem cells, exhibit a no. of defects in leukocyte behavior, including elevated nos. of circulating neutrophils, virtually total absence of leukocyte rolling in mesenteric venules, and delayed recruitment of neutrophils to the peritoneal cavity upon exptl. induced inflammation. These results clearly demonstrate a role for P selectin in leukocyte interactions with the vessel wall and in the early steps of leukocyte recruitment at sites of inflammation. These mutant mice should prove useful in deciphering the contributions of P selectin in various inflammatory responses as well as in platelet functions.

L66 ANSWER 41 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1993:446915 Document No. 119:46915 Endothelial-leukocyte adhesion molecules. Possible role in monocyte recruitment into **atherosclerotic** lesions. Kume, Noriaki (Brigham Women's Hosp., Harvard Med. Sch., Boston, MA, 02115, USA). Mol. Med. (Tokyo), 30(3), 312-17 (Japanese) 1993. CODEN: MOLMEL.

AB A review with 35 refs., focusing on the interaction of the adhesion mols. expressed on the endothelial cells (VCAM-1, ICAM-1, E- and **P-selectin**) and those expressed on the leukocytes [VLA-4, Mac-1 (CD11b/CD18), **sialyl Lewis**-X, and L-selectin], and also on a multi-stage model of the mechanism of monocyte adhesion to vascular endothelium.

L66 ANSWER 42 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1993:470292 Document No. 119:70292 Interaction of LAM-1 with an inducible ligand supports leukocyte adhesion to endothelium. Kansas, Geoffrey S.; Spertini, Olivier; Luscinskas, Francis W.; Gimbrone, Michael; Tedder, Thomas F. (Dana Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA). Struct., Funct. Regul. Mol. Involved Leukocyte Adhes. [Proc. Int. Conf.], 2nd, Meeting Date 1991, 168-81. Editor(s): Lipsky, Peter E. Springer: New York, N. Y. (English) 1993. CODEN: 59CPAD.

AB Evidence is presented that LAM-1, in addn. to its well-known role in mediating the binding of lymphocytes to the high endothelial venules (HEV) of peripheral lymph nodes is also important in the binding of

leukocytes to endothelium at sites of inflammation. Specifically, it is proposed that LAM-1 mediates the initial attachment of all classes of leukocytes to endothelium at sites of inflammation, and that this adhesion is mediated through a novel, inducible glycoprotein.

L66 ANSWER 43 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
94045633 EMBASE Endothelial-leukocyte adhesive interactions in inflammatory diseases. Munro J.M.. Department of Histopathology, University College London, Medical School, University Street, London WC1E 6JJ, United Kingdom. EUR. HEART J. 14/SUPPL. K (72-77) 1993. ISSN: 0195-668X. CODEN: EHJODF. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB There is evidence that vascular endothelium directs the accumulation of leukocytes in inflammation through various means, particularly by the expression of specific cell surface molecules which are adhesive for ligands on circulating leukocytes. Examples of such molecules are E-selectin and intercellular adhesion molecule 1 (ICAM-1) In an experimental model of various forms of inflammation, E-selectin and ICAM-1 were induced in association with adhesion and emigration of circulating polymorphonuclear and mononuclear leukocytes. Further work in humans showed endothelium to express E-selectin in inflammation. In addition, the presence of a leukocyte ligand for E-selectin, sialyl-Lewis X has been seen on cells accumulating in inflammation. Furthermore, sialyl-Lewis X was also unexpectedly seen on endothelium. The role of sialyl-Lewis X on endothelium is as yet uncertain although it may function as an adhesion receptor for leukocytes. Other endothelial adhesion receptors, such as vascular cell adhesion molecule 1 (VCAM-1), are described. Atherosclerosis shows many features in common with inflammation. These are discussed, and the demonstrated and potential relevance of endothelial adhesive phenomena in routine inflammation to those in atherosclerosis are reviewed. For example, a VCAM-1 homologue has been described on the endothelium over evolving atherosclerotic lesions in rabbits.

L66 ANSWER 44 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1994:103735 Document No. 120:103735 Potential roles for oxidized phospholipids in inflammation and atherogenesis. Prescott, Stephen M.; Patel, Kamala D.; Smiley, Patricia L.; Stafforini, Diana M.; Lorant, Diane E.; Zimmerman, Guy A.; McIntyre, Thomas M. (Nora Eccles Harrison Cardiovasc. Res. Train. Inst., Univ. Utah, Salt Lake City, UT, 84112, USA). Atheroscler. Rev., 25(Atherosclerosis), 59-68 (English) 1993. CODEN: ATHEDF. ISSN: 0362-1650.

AB A review, with 15 refs., on: **P-selectin** and platelet-activating factor (PAF) act coordinately in the rapid adhesion of leukocytes to endothelial cells; endothelial cells exposed to oxidants express **P-selectin** and release bioactive oxidized phospholipids; and PAF acetylhydrolase hydrolyzes oxidized phospholipids and blocks modification of low-d. lipoprotein.

L66 ANSWER 45 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
93104582 EMBASE Platelet .alpha.-granules. Harrison P.; Cramer E.M.. Coagulation Research, Rayne Institute St, Thomas' Hospital, London SE1 7EH, United Kingdom. BLOOD REV. 7/1 (52-62) 1993. ISSN: 0268-960X. CODEN: BLOREB. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Platelets contain a vast number of biologically active molecules within cytoplasmic granules which are classified according to their respective distinct ultrastructures, densities and content. The .alpha.-granule is a unique secretory organelle in that it exhibits further compartmentalization and acquires its protein content via two distinct mechanisms: (1) biosynthesis predominantly at the megakaryocyte (MK) level (with some vestigial platelet synthesis) (e.g. platelet factor 4) and (2) endocytosis and pinocytosis at both the MK and circulating platelet levels (e.g. fibrinogen (Fg) and IgG). The currently known list of .alpha.-granular proteins continues to enlarge and includes many adhesive proteins (e.g. Fg,

von Willebrand factor (vWf) and thrombospondin (TSP)), plasma proteins (e.g. IgG and albumin), cellular mitogens (e.g. platelet derived growth factor and TGF.beta.), coagulation factors (e.g. factor V) and protease inhibitors (e.g. .alpha.2-macroglobulin and .alpha.2-antiplasmin). More recently the inner lining of the .alpha.-granule unit membrane has been demonstrated to contain a number of physiologically important receptors including glycoprotein IIb/IIIa (.alpha.IIb.beta.3) and P-selectin. The .alpha.-granules originate from small precursor granules which can be observed budding from the trans-Golgi network within the platelet precursor cell, the MK. During MK maturation the .alpha.-granules become very prominent and are ultimately packaged into platelets during thrombopoiesis. The .alpha.-granular contents are destined for release during platelet activation at sites of vessel wall injury and thus play an important role in haemostasis, inflammation, ultimate wound repair and in the pathogenesis of atherosclerosis.

L66 ANSWER 46 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
93330014 EMBASE Leukocyte adhesion molecules on the vascular endothelium: Their role in the pathogenesis of cardiovascular disease and the mechanisms underlying their expression. Sluiter W.; Pietersma A.; Lamers J.M.J.; Koster J.F.. Department of Biochemistry, Cardiovascular Research Institute, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, Netherlands. J. CARDIOVASC. PHARMACOL. 22/SUPPL. 4 (S37-S44) 1993. ISSN: 0160-2446. CODEN: JCPCDT. Pub. Country: United States. Language: English. Summary Language: English.

AB It is well known that granulocytes increase infarct size after reperfusion of the ischemic myocardium, and that monocytes promote atherogenesis. Those cells are also believed to play a contributory role in pathogenesis of coronary restenosis as response to arterial injury during balloon angioplasty. The adhesion of those leukocytes to the vascular endothelium is a prerequisite for their recruitment and accumulation in the lesion. Inflammatory mediators likely to occur under those conditions, e.g., histamine, thrombin, oxygen-derived free radicals (ODFR), interleukin (IL)- I, tumor necrosis factor (TNF)-.alpha., and activated complement factors, induce in a distinct time course the (transient) expression of the leukocyte adhesion molecules P-selectin, E-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1 on the endothelium. Only VCAM-1 is specific for monocytes; the others mediate the binding and subsequent extravasation of both monocytes and granulocytes. The response to the relevant inflammatory mediators, except for extracellularly produced ODFR, is coupled via specific receptors on the surface of the endothelium to specific signal transduction pathways and, except for P-selectin (early response), is directly dependent on protein synthesis (intermediate and late response). Protein kinase-C-induced phosphorylation of transcription factors is often shown to be involved. Protein synthesis is preceded by increased transcription of mRNA that is regulated in part by the transcription factor NF-.kappa.B. Indications have been obtained that intracellularly produced ODFR may be involved in the translocation of this transcription factor. This rapidly increasing insight into the mechanisms by which granulocytes and monocytes adhere to the vascular endothelium will open new avenues to therapeutic strategies to alleviate tissue damage in cardiovascular diseases.

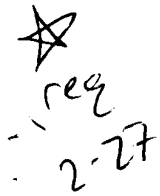
L66 ANSWER 47 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1993:537327 Document No. 119:137327 Leukocyte-associated cell surface protein LAM-1 (leukocyte adhesion molecule-1). Tedder, Thomas F. (Dana-Farber Cancer Institute, Inc., USA). PCT Int. Appl. WO 9220712 A1 921126, 29 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MW, NL, NO, PL, RO, RU, SD, SE; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 92-US3970 920513. PRIORITY: US 91-700773 910515.

AB LAM-1, contg. domains homologous with binding domains of animal

lectins, growth factors, and C3/C4 binding proteins; the specific domains of LAM-1; and the genomic DNA sequences encoding LAM-1 are disclosed. LAM-1, or a domain thereof, or an antagonist to LAM-1 or domain thereof are used in therapeutic agents to treat human patients suffering from a leukocyte-mobilizing condition. The patient suffers from, e.g., tissue damage, autoimmune disorder, cancer, or organ or tissue transplant. B-cell-specific cDNAs were isolated from a human tonsil cDNA library and cDNA encoding the LAM-1 protein was identified, cloned, and sequenced. The structure of the lyam-1 gene, which encodes the LAM-1 protein, was detd. for exons II-X.

L66 ANSWER 48 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1992:626325 Document No. 117:226325 Method of inhibiting **platelet** activation-dependent **granule**-external **membrane protein** (**PADGEM**)-mediated interactions using an inhibitor comprising a 2,6-linked **sialic** acid component. Furie, Bruce; Furie, Barbara C.; Larsen, Eric; Palabrica, Theresa; Sajer, Susan; Gilbert, Gary E.; Wagner, Denisa D.; Celi, Alessandro; Erban, John; Gibson, Rosemary (New England Medical Center Hospitals, Inc., USA). PCT Int. Appl. WO 9216612 A2 921001, 57 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 92-US1915 920309. PRIORITY: US 91-667453 910311.

AB A method is disclosed for inhibiting (reducing or preventing) the interaction of a **PADGEM**-bearing cell with a cell bearing a **PADGEM** ligand by contacting the **PADGEM**-bearing cell with an inhibitor comprising a 2,6-linked **sialic** acid component. Using the inhibitor of the invention, it is possible to inhibit the interaction of e.g. a platelet or endothelial cell with e.g. a leukocyte. The inhibitor, which has an **Lex** core, is useful for treating **atherosclerosis**, thrombosis, etc. Lacto-N-fucopentaose III [Gal.beta.1.fwdarw.4(Fuco.alpha.1.fwdarw.3) GlcNac.beta.1.fwdarw.3Gal.beta.1.fwdarw.4Glc] inhibited adherence of activated platelets to neutrophils; half-maximal inhibition was obsd. at .apprx.50 .mu.g/mL.



L66 ANSWER 49 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1993:512963 Document No. 119:112963 Aptamers specific for biomolecules and method of making them. Toole, John J.; Griffin, Linda C.; Bock, Louis C.; Latham, John A.; Muenchau, Daryl Dean; Krawczyk, Steven (Gilead Sciences, Inc., USA). PCT Int. Appl. WO 9214843 A1 920903, 83 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 92-US1383 920221. PRIORITY: US 91-658796 910221; US 91-658849 910221; US 91-659103 910221; US 91-659113 910221; US 91-659114 910221; US 91-659980 910221; US 91-659981 910221; US 91-744870 910814; US 91-745215 910814; US 91-787921 911106.

AB A method for identifying oligomer sequences which specifically bind target mols. (serum proteins, kinins, eicosanoids, etc.) is described. The technique involves complexation of the target mol. with a mixt. of oligonucleotides contg. random sequences and sequences which serve as PCR primers under conditions in which a complex is formed with the specifically binding sequences, but not with the other members of the oligonucleotide mixt. The complex is then sepd. from uncomplexed oligonucleotides, and the complexed members of the oligonucleotide mixt. are recovered from the sepd. complex using PCR. The recovered oligonucleotides may be sequenced, and successive rounds of selection using complexation, sepn., amplification, and recovery can be employed. The oligonucleotides can be used for therapeutic and diagnostic purposes. The method is used to generate aptamers that bind serum factor X, thrombin, bradykinin, and prostaglandin F2.alpha.. Aptamer specificity for binding to and inhibition of thrombin was demonstrated.

L66 ANSWER 50 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1992:440451 Document No. 117:40451 Treatment for inflammatory bowel disease with antibody or other molecule recognizing ELAM-1 (endothelial cell-leukocyte adhesion mol.-1) protein. Lobb, Roy R.; Podolsky, Daniel K. (Biogen, Inc., USA; General Hospital Corp.). PCT Int. Appl. WO 9208489 A1 920529, 21 pp. DESIGNATED STATES: W: AU, CA, JP, KR, NO; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE. (English). CODEN: PIXXD2. APPLICATION: WO 91-US8257 911106. PRIORITY: US 90-610512 901108.

AB Inflammatory bowel disease (IBD) is treated by administration of an antibody, polypeptide, or other mol. recognizing ELAM-1, a protein induced on the surface of endothelial cells. A method for ex vivo imaging of IBD with the above antibody or other mol. is also claimed. ELAM-1 was shown to be produced in the endothelial cells of active IBD tissue.

L66 ANSWER 51 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1992:446529 Document No. 117:46529 **P-selectin** and E-selectin. Distinct but overlapping leukocyte ligand specificities. Larsen, Glenn R.; Sako, Dianne; Ahern, Tim J.; Shaffer, Mary; Erban, John; Sajer, Susan A.; Gibson, Rosemary M.; Wagner, Denisa D.; Furie, Barbara C.; Furie, Bruce (Genet. Inst. Inc., Cambridge, MA, 02140, USA). J. Biol. Chem., 267(16), 11104-10 (English) 1992. CODEN: JBCHA3. ISSN: 0021-9258.

AB **P-selectin** on platelets and endothelial cells and E-selectin on endothelial cells are leukocyte receptors that recognize lineage-specific carbohydrates on neutrophils and monocytes. The proposed ligands for these receptors contain the Lex core and sialic acid. Since other investigators have shown that both E-selectin and **P-selectin** bind to sialylated Lex, it was evaluated whether E-selectin and **P-selectin** recognize the same counter-receptor on leukocytes. The interaction of HL60 cells with Chinese hamster ovary (CHO) cells expressing **P-selectin** or E-selectin was studied. To det. whether a protein component is required in addn. to sialyl Lex for either **P-selectin** or E-selectin recognition, HL60 cells or neutrophils were digested with proteases, including chymotrypsin, elastase, proteinase Glu-C, ficin, papain, or thermolysin. Cells treated with these proteases bound E-selectin but not **P-selectin**. Fucosidase or neuraminidase treatment of HL60 cells markedly decreased binding to both E-selectin- and **P-selectin**-expressing CHO cells. Growth of HL60 cells in tunicamycin inhibited the ability of these cells to support **P-selectin**-mediated binding and, to a lesser extent, E-selectin-mediated binding. Purified **P-selectin** inhibited CHO:**P-selectin** binding to HL60 cells, but incompletely inhibited CHO:E-selectin binding to HL60 cells. However, purified sol. E-selectin inhibited CHO:**P-selectin** and CHO:E-selectin binding to HL60 cells equivalently and completely. COS cells, unable to bind to E-selectin or **P-selectin**, bound E-selectin but not **P-selectin** upon transfection with .alpha.-1,3-fucosyltranserase or .alpha.-1,3/1,4-fucosyltransferase. Similarly, LEC 11 cells expressing sialyl Lex bound E-selectin- but not **P-selectin**-expressing CHO cells. Sambucus nigra lectin, specific for the sialyl-2,6.beta.Gal/GalNAc linkage, inhibited **P-selectin** but not E-selectin binding to HL60 cells. Although sialic acid and Lex are components of the **P-selectin** ligand and the E-selectin ligand, these results indicate that the ligands are related, having overlapping specificities, but are structurally distinct. A protein component contg. sialyl Lex in proximity to sialyl-2,6.beta.Gal structures on the **P-selectin** ligand may contribute to its specificity of **P-selectin**.

L66 ANSWER 52 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1993:78883 Document No. 118:78883 CD4 changes conformation upon ligand binding. Szabo, Gabor, Jr.; Pine, P. Scott; Weaver, James L.; Rao,

Patricia E.; Aszalos, Adorjan (Cent. Drug Eval. Res., FDA, Washington, DC, 20204, USA). J. Immunol., 149(11), 3596-604 (English) 1992. CODEN: JOIMA3. ISSN: 0022-1767.

AB Aurintricarboxylic acid (ATA) has been shown to block the binding site for both HIV gp120 and mAb anti-Leu 3a on CD4. It was unexpectedly found that brief treatment with .gtoreq.1 .mu.g/mL ATA rapidly disengages another mAb, OKT4E, after it has been bound to CD4 on human PBL. OKT4E is specific for a discontinuous epitope overlapping the MHC class II-binding region in the N-terminal CD4 domain. Interestingly, among 10 other mAb tested, only anti-Leu 8, specific for a leukocyte homing receptor is also quickly released from the cells by ATA treatment. Disengagement of the OKT4E mAb is also seen on a CD4-pos. cell line (HPB-ALL) and with recombinant sol. CD4 (sCD4) bound to immobilized OKT4E. In all of these cases, disengagement is prevented if OKT4E is cross-linked, or the Leu 3a site is blocked by the mAb, but not by gp120. Photobleaching fluorescence resonance energy transfer (pFRET) measurements suggest that OKT4E is released as an indirect consequence of ATA-evoked conformational changes of CD4. Similar changes were detected as a result of gp120 binding to PBL. These data raise the possibility of a novel type of immunomodulation: induced disengagement of a bound ligand from its antigen.

L66 ANSWER 53 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1993:78770 Document No. 118:78770 Adhesion molecules in **atherosclerosis** and myocardial ischemia-reperfusion injury. Abe, Yasunori; Kawakami, Masanobu (Omiya Med. Cent., Jichi Med. Sch., Omiya, 330, Japan). Saishin Igaku, 47(12), 2306-12 (Japanese) 1992. CODEN: SAIGAK. ISSN: 0370-8241.

AB A review with 40 refs., on the adhesion mols. (AM) on the vessel endothelial cells, and the roles of AM in **atherosclerosis** and reperfusion injury. Expression and functions of ICAM 1, ICAM-110/VCAM 1, ELAM 1 (E selectin), and **GMP-140** (**P-selectin**) are discussed. VCAM 1 and ICAM 1 are expressed in **atherosclerosis** of rabbit and human, resp. ICAM 1 and ELAM 1 are important in onset on reperfusion injury.

L66 ANSWER 54 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.

93151574 EMBASE Blood monocyte adhesion to vascular endothelial cells. Implication in vascular pathology. Dosquet C.; Wautier J.-L.. Lab de Biologie Vasculaire/, Cellulaire, Hopital Lariboisiere, 2 rue Ambroise Pare, 75010 Paris, France. CLIN. HEMORHEOL. 12/6 (817-829) 1992. ISSN: 0271-5198. CODEN: CLHEDF. Pub. Country: United States. Language: English. Summary Language: English.

AB The blood monocytes adhere to endothelial cells unstimulated and after stimulation by interleukin-1, tumor necrosis factor or other mediators. This process is mediated through specific molecules on both endothelial cells and monocytes. Using specific monoclonal antibodies and molecular cloning several families of molecules involved in leukocyte-endothelial cell interaction have been defined. Leukocyte adhesion molecules include the three .beta.2 integrins (CD11/CD18 molecules), VLA-4 and the L-Selectin. E-Selectin (ELAM-1), P-Selectin (GMP-140) and receptors of the immunoglobulin superfamily (ICAM-1, ICAM-2 and VCAM-1) are expressed on endothelial cells in basal conditions and after activation by cytokines. It has been shown that these adhesive molecules are involved in blood monocyte adhesion to endothelial cells in vitro. The in vivo expression of these adhesive molecules on the vascular endothelium has been described in acute and chronic inflammatory situations such as Kawasaki syndrome and atherosclerosis.

L66 ANSWER 55 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1993:36695 Document No. 118:36695 Viral activation of the coagulation cascade. Etingin, Orli R.; Silverstein, Roy L.; Hajjar, David P. (Med. Coll., Cornell Univ., New York, NY, 10021, USA). Semin. Virol., 3(2), 125-33 (English) 1992. CODEN: SEVIEL. ISSN: 1044-5773.

AB A review with 39 refs. **Atherosclerotic** lesions in animals

and humans have been reported to contain herpesviral genomic material during different stages of development. For this reason, it has been hypothesized that latent viral infections may be an early trigger in this arteriopathy. Because viral proteins can manifest fibrin deposition in the vessel wall, the authors and others have tested the hypothesis that herpes simplex virus infection can predispose human endothelial cells to become procoagulant and attract inflammatory cells, perhaps by elaborating specific cell receptors on the surface of the vessel wall. The composite of work highlighted in this review article provides documentation that viral infection can enhance coagulation processes, and can render the endothelium pro-thrombotic. The authors provide evidence that the herpesvirus infected endothelium, once activated or injured, can serve as a template by expressing receptors for circulating monocytes and neutrophils which can predispose to lipid accumulation and inflammation within the vessel wall. These findings support a role of herpesviruses in **atherosclerotic** and thrombotic diseases.

L66 ANSWER 56 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1992:488079 Document No. 117:88079 Granule membrane protein 140 (**GMP-140**). Larsen, Eric (Dartmouth Med. Sch., Hanover, NH, 03756, USA). Trends Glycosci. Glycotechnol., 4(15), 25-31 (English/Japanese) 1992. CODEN: TGGLEE. ISSN: 0915-7352.
AB A review with 53 refs. **GMP-140**, a member of the selectin family of adhesion mols., is a receptor for neutrophils and monocytes that is expressed on the surface of activated platelets and endothelial cells. The corresponding ligand on leukocytes involves a carbohydrate structure, including the CD15 antigen, lacto-N-fucopentaose III. **GMP-140** mediated cell binding is likely crit. in the hemostatic and inflammatory response to tissue and vascular injury. In addn., these interactions may be important in pathol. processes such as **atherosclerosis** or metastasis. Future investigations should elucidate structure-function relationships of **GMP-140** and its ligand as well as the cellular consequences of adhesion.

L66 ANSWER 57 OF 61 EMBASE COPYRIGHT 1996 ELSEVIER SCI. B.V.
93331518 EMBASE Neutrophils and peripheral arterial disease. Nash G.; Shearman C.. Department of Haematology, Univ of Brimingham Medical School, Birmingham, United Kingdom. CRIT. ISCHAEMIA 2/1 (4-13) 1992. ISSN: 0956-2257. CODEN: CRISE3. Pub. Country: United Kingdom. Language: English. Summary Language: English.

L66 ANSWER 58 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1992:228245 Document No. 116:228245 Selectin-binding intercellular adhesion mediators for pharmaceuticals. Paulson, James C.; Perez, Mary S.; Gaeta, Federico C. A.; Ratcliffe, Robert Murray (Cytel Corp., USA). PCT Int. Appl. WO 9119502 A1 911226, 108 pp. DESIGNATED STATES: W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, PL, RO, SD, SE, SU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IT, LU, ML, MR, NL, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 91-US4284 910614. PRIORITY: US 90-538853 900615; US 90-619319 901128; US 90-632390 901221; WO 91-US3592 910522.
AB Compns. and methods for reducing or controlling inflammation and for treating inflammatory disease processes and other pathol. conditions mediated by selectin-mediated intercellular adhesion are disclosed. The pharmaceutical compns. comprise a carrier and compds. which selectively bind selectin, e.g. biomols. contg. R1Gal.beta.1,4(Fuc.alpha.1,3)GlcNAcR2a [R1 = oligosaccharide, R3R4C(CO2H); R3, R4 = H, C1-8 alkyl, hydroxyl C1-8 alkyl, aryl C1-8 alkyl, alkoxy C1-8 alkyl; R2 = .beta.1,3Gal, .perp.,2Man, .alpha.1,6GalNAc; a = 0,1]. Rats were protected from endotoxic shock by treatment with monoclonal antibody P6E2 to human ELAM-1 protein.

L66 ANSWER 59 OF 61 HCAPLUS COPYRIGHT 1996 ACS
1991:556203 Document No. 115:156203 Identification of a monocyte

receptor on herpesvirus-infected endothelial cells. Etingin, Orli R.; Silverstein, Roy L.; Hajjar, David P. (Med. Coll., Cornell Univ., New York, NY, 10021, USA). Proc. Natl. Acad. Sci. U. S. A., 88(16), 7200-3 (English) 1991. CODEN: PNASA6. ISSN: 0027-8424.

AB The adhesion of circulating blood cells to vascular endothelium may be an initial step in **atherosclerosis**, inflammation, and wound healing. One mechanism for promoting cell-cell adhesion involves the expression of adhesion mols. on the surface of the target cell. Herpes simplex virus infection of endothelium induces arterial injury and has been implicated in the development of human **atherosclerosis**. The present study demonstrates that HSV-infected endothelial cells express the adhesion mol. **GMP140** and that this requires cell surface expression of HSV glycoprotein C and local thrombin generation. Monocyte adhesion to HSV-infected endothelial cells was completely inhibited by anti-**GMP140** antibodies but not by antibodies to other adhesion mols. such as VCAM and ELAM-1. The induction of **GMP140** expression on HSV-infected endothelium may be an important pathophysiol. mechanism in virus-induced cell injury and inflammation.

L66 ANSWER 60 OF 61 MEDLINE

91084956 In vivo technetium-99m S12 antibody imaging of platelet alpha-granules in rabbit endothelial neointimal proliferation after angioplasty. Miller D D; Boulet A J; Tio F O; Garcia O J; Guy D M; McEver R P; Palmaz J C; Pak K Y; Neblock D S; Berger H J; et al. (Department of Medicine, University of Texas Health Science Center, San Antonio 78284-7872..)CIRCULATION, (1991 Jan) 83 (1) 224-36. Journal code: DAW. ISSN: 0009-7322. Pub. country: United States. Language: English.

AB To examine the specificity of technetium-99m monoclonal antibody (S12) imaging for identifying activated platelets at interventional injury sites in atherosclerotic rabbit arteries, subgroups of unheparinized rabbits (n = 39) underwent serial percutaneous transluminal aortic angioplasty (PTA) procedures (with or without intravascular stent placement) followed by in vivo and then ex vivo gamma camera imaging, scanning, and immunoelectron microscopy to determine the intravascular loci of S12 Fab' antibody binding. Despite angiographic vessel patency, image-derived ratios of in vivo S12 binding in injured versus uninjured vascular segments were significantly increased (p less than 0.05) after one PTA (1.3 +/- 0.17, n = 7), PTA twice at 6-week intervals (1.4 +/- 0.22, n = 7), and PTA plus stent placement (1.6 +/- 0.28, n = 7) compared with control experiments (1.1 +/- 0.13, n = 7). Ex vivo imaging of blood-free excised aortas confirmed S12 localization at PTA (2 +/- 0.4, n = 3) and PTA plus stent placement (5 +/- 3.8, n = 7) sites (both p less than 0.05 versus controls). S12 antibody uptake decreased significantly (p less than 0.05) at 1 week after PTA plus stent placement in vivo (1.1 +/- 0.10, n = 4) and ex vivo (1.6 +/- 0.7, n = 3). Electron microscopic studies confirmed dense platelet, fibrin, and red blood cell deposition in regions of acute injury, with endothelial neointimal proliferation at 1 week after PTA. Immunoelectron microscopic studies confirmed specific in vivo S12 binding (22:1 versus nonrelevant IgG) at sites of alpha-granule GMP-140 expression in activated platelets. Therefore, S12 studies may be useful to localize sites of platelet-derived mitogen release at arterial PTA injury sites.

L66 ANSWER 61 OF 61 HCAPLUS COPYRIGHT 1996 ACS

1985:468951 Document No. 103:68951 Zinc-induced platelet aggregation is mediated by the fibrinogen receptor and is not accompanied by release or by thromboxane synthesis. Heynes, Anthon du P.; Eldor, Amiram; Yarom, Rena; Marx, Gerard (Dep. Hematol., Hadassah Univ. Hosp., Jerusalem, 91120, Israel). Blood, 66(1), 213-19 (English) 1985. CODEN: BLOOAW. ISSN: 0006-4971.

AB Zn (0.1-0.3 mM) induces aggregation of washed human **platelet** suspensions. Higher concns. (1-3 mM) of Zn were needed to aggregate **platelets** in **platelet**-rich plasma obtained from blood anticoagulated with low-mol.-wt. **heparin**, probably

due to the binding of Zn to the plasma **proteins**. Zn-induced aggregation of normal washed **platelets** required added fibrinogen and no aggregation occurred with thrombasthenic **platelets** or with normal **platelets** pretreated with a monoclonal antibody (10E5) that blocks the **platelet** fibrinogen receptor. Apparently the **platelet membrane** fibrinogen receptor-**glycoproteins** IIb and IIIa mediate the effect of Zn. Zn-induced aggregation was blocked by the agent TMB-8, which interferes with the internal Ca2+ flux, and by prostacyclin, which elevates **platelet** cAMP levels. Zn-induced aggregation was not accompanied by thromboxanes synthesis or by the secretion of dense-body serotonin and was not affected by preexposure of **platelets** to acetylsalicylic acid. Expts. with creatine phosphate/creatine phosphokinase showed that the Zn effect on **platelets** was independent of extracellular ADP. Zn had an additive effect when **platelet** aggregation was stimulated with subthreshold concns. of collagen or ADP. Together with the known effects of nutritional Zn on in vivo bleeding, **platelet** aggregation, and lipid metab., the results suggest that Zn may have an important bearing on normal hemostasis, thrombosis, and **atherosclerosis**.